Phase 1b/2 study of ivosidenib plus durvalumab and gemcitabine/cisplatin as first-line therapy in patients with locally advanced, unresectable or metastatic cholangiocarcinoma with an IDH1 mutation: safety lead-in results

Do-Youn Oh,[1] Anthony El-Khoueiry,[2] Dominik Modest,[3] Hong Jae Chon,[4] Hye Jin Choi,[5] Eric Assenat,[6] Mohamed Bouattour,[7] Valentine Barboux,[8] Camelia Gliser,[9] Nicole McNeer,[9] James Harding[10]

1. Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; 2. University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA, USA; 3. Department of Hematology, Oncology and Cancer Immunology, Charité-Universitätsmedizin Berlin, Berlin, Germany; 4. Department of Medical Oncology, CHA Bundang Medical Center, CHA University, Seongnam, South Korea; 5. Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; 6. Medical Oncology Department, Montpellier Cancer Institute (ICM), University of Montpellier, Montpellier, France; CHU Montpellier, University of Montpellier, Montpellier, France; 7. Department of Liver Cancer and Innovative Therapy Unit, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France; 8. Servier Research Institute, Gif-sur-Yvette, France; 9. Servier BioInnovation, Boston, MA, USA; 10. Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Contact: Do-Youn Oh, MD, PhD, ohdoyoun@snu.ac.kr

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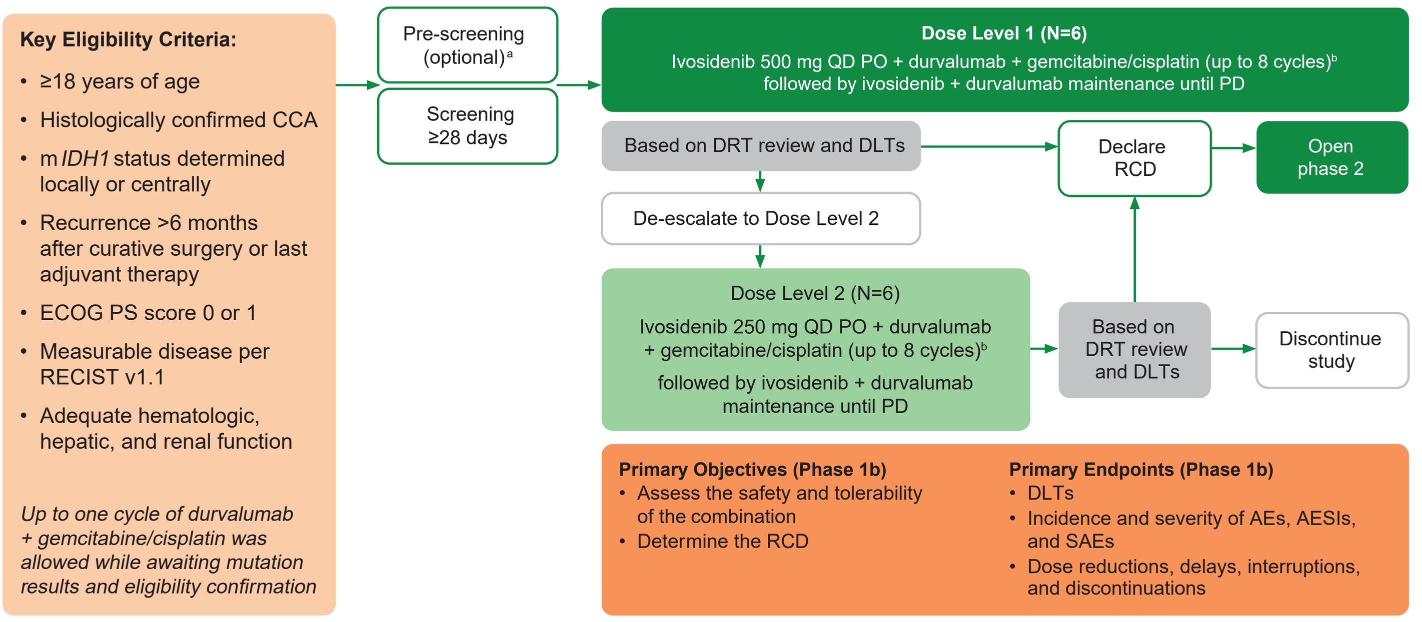
Background

- Cholangiocarcinomas (CCAs) are rare and aggressive cancers with a poor prognosis; the 5-year overall survival rates regardless of stage of diagnosis are 9%–10%, and only 2% in patients with distant metastases[1]
- Early-stage disease is generally asymptomatic, and most patients present with locally advanced, unresectable or metastatic disease at diagnosis[2]
- The only approved therapy and standard of care (SOC) for first line, locally advanced unresectable or metastatic CCA is chemotherapy (gemcitabine and cisplatin) in combination with immunotherapy (durvalumab or pembrolizumab)[3,4]
  – In the phase 3 TOPAZ-1[3] and KEYNOTE-966[4] studies, adding durvalumab or pembrolizumab, respectively, to chemotherapy significantly improved overall survival compared with chemotherapy alone.
- Ivosidenib is a first-in-class, oral, targeted, small-molecule inhibitor of mutated isocitrate dehydrogenase 1 (m*IDH1*) that is approved in 48 countries for the treatment of adults with previously treated locally advanced or metastatic m*IDH1* CCA[6,7]
- Recent studies suggest mIDH1 leads to repression of key immune-related genes, impairing lymphocyte infiltration and ivosidenib stimulates T cell recruitment and effector function in preclinical CCA models.[8-11] Inhibition of mIDH1 in combination with SOC in earlier stages of disease may improve clinical benefit
- This is a multicenter phase 1b/2 study (NCT06501625) of ivosidenib in combination with durvalumab and gemcitabine/cisplatin as first-line therapy in patients with locally advanced, unresectable or metastatic CCA with m*IDH1*
  – Here, we report the results from the safety lead-in phase (phase 1b). Phase 2 is open and ongoing

Methods

- Phase 1b (safety lead-in phase) of the study was designed to establish the recommended combination dose (RCD) for phase 2 (expansion phase)



Data cutoff: July 10, 2025. [a]Pre-screening was available for determining the *mIDH* status. [b]Up to 7 cycles if durvalumab + gemcitabine/cisplatin was administered prior to study treatment initiation.AE, adverse event; AESI, AE of special interest; CCA, cholangiocarcinoma; DLT, dose-limiting toxicity; DRT, data review team; ECOG PS, Eastern Cooperative Oncology Group performance status; mIDH1, mutant isocitrate dehydrogenase 1; PD, progressive disease; PO, orally; QD, daily; RCD, recommended combination dose; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious AE.

- Dose-limiting toxicity (DLT) was defined as any clinically significant adverse event (AE) observed during the first 21 days of dosing (through cycle 1) following administration of study treatment; assessed as not related to disease progression, concomitant medications and considered related to study drugs
- DLTs were assessed by investigators and reviewed by the data review team. DLT evaluability was determined by:
  – Patients who received at least 1 full dose of durvalumab, gemcitabine, and cisplatin each and at least 75% of the planned dose of ivosidenib in cycle 1
  – Patients who received the combination therapy and experienced a DLT through cycle 1
- A minimum of 6 DLT-evaluable patients treated at a combination dose were required to declare the RCD for the phase 2 part of the study
- If <33% of DLT-evaluable patients (eg, 0 or 1 patient/6 DLT-evaluable patients) experienced a DLT during the first cycle at the 500 mg daily (QD) or the 250 mg QD dose level, and the nature of the event(s) was not deemed a significant risk, the study will proceed to phase 2
- Any QT prolongation event grade 2, irrespective of the seriousness of the event, was defined as an AE of special interest (AESI)

Results

- As of July 10, 2025, enrollment in phase 1b was complete, with 7 patients enrolled in the US, Germany, France, and South Korea
- Six patients remain on treatment and 1 patient discontinued due to an AE
- Duration of treatment ranged between 1 and 4 months

Baseline patient demographics and disease characteristics

Demographics and disease characteristics	All patients (N=7)
Age, years (range)	37–75
Sex, n (%)	
Male	4 (57.1)
Female	3 (42.9)
ECOG PS, n (%)	
0	5 (71.4)
1	2 (28.6)
m*IDH1* allele, n	
R132C/R132L/R132G/R132H/R132S	3/2/2/0/0
Cholangiocarcinoma type, n (%)	
Intrahepatic	7 (100)
Extrahepatic	0
Extent of disease, n (%)	
Locally advanced	1 (14.3)
Metastatic	6 (85.7)
Hepatitis B, n (%)	
Yes	1 (14.3)
No	6 (85.7)
1 prior cycle of durvalumab/gemcitabine/cisplatin, n (%)	
Yes	3 (42.9)
No	4 (57.1)

ECOG PS, Eastern Cooperative Oncology Group performance status; m*IDH1*, mutant isocitrate dehydrogenase 1.

Safety

TEAEs	All patients, N=7 n (%)
DLTs	1 (16.7)[c]
Any grade TEAEs	7 (100)
Grade 1/2 TEAEs	6 (85.7)
Grade 3 TEAEs	6 (85.7)
Neutrophil count decreased[a]	4 (57.1)
Cholangitis	1 (14.3)
Drug-associated liver injury	1 (14.3)
QT prolongation	1 (14.3)
Hypomagnesemia	1 (14.3)
SAEs	2 (28.6)
Cholangitis	1 (14.3)
Drug-associated liver injury	1 (14.3)
AESIs	1 (14.3)
TEAEs leading to interruption and/or delay of study drug	4 (57.1)
Interruption of ivosidenib	1 (14.3)
Delay of gemcitabine/cisplatin	2 (28.6)
Interruption or delay of all drugs	1 (14.3)
TEAEs leading to reduction of study drug[b]	1 (14.3)
TEAEs leading to study drug discontinuation	1 (14.3)

[a]There was only one grade 4 TEAE (neutrophil count decrease). [b]Reduction of gemcitabine. [c]Percentage based on 6 patients evaluable for DLT. AESI, adverse event of special interest; DLT, dose-limiting toxicity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

DLT — 16.7% (1/6 PATIENTS)
- Six of the 7 patients enrolled were DLT evaluable
  – One patient was not DLT evaluable due to receiving <75% of the planned ivosidenib dose in cycle 1 without a DLT. Patient remains on treatment but was replaced per protocol
- Grade 3 drug-associated liver injury, with elevated transaminases and bilirubin, occurred in 1 patient and was considered related to ivosidenib, gemcitabine, and cisplatin
- All study drugs were interrupted; a liver biopsy indicated combined damage from a pre-existing condition (fatty liver and prior HCV infection) and acute toxicity. Study drugs were discontinued; the patient fully recovered

Most Common Grade≥3 TEAE — 67.1% (4/7 PATIENTS)
- The most common Grade≥3 TEAE was neutrophil count decreased
  – Grade 3 in 3 patients;
  – Grade 4 in 1 patient. This was the only Grade 4 event reported in the study

SAEs — 28.6% (2/7 PATIENTS)
- Cholangitis (n=1); not related to study drugs. Resolved without treatment modification
- Drug-associated liver injury (n=1); considered related to ivosidenib and gemcitabine/cisplatin; met criteria for DLT. All study drugs were discontinued

AESI — 14.3% (1/7 PATIENTS)
- Asymptomatic Grade 3 QT prolongation
- Ivosidenib was interrupted, and the event resolved to Grade 1 within 7 days
- Ivosidenib was restarted at 250 mg QD; following electrolyte optimization, the dose was re-escalated to the full 500 mg QD

AESI, adverse event of special interest; DLT, dose-limiting toxicity; HCV, hepatitis C virus; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- Ivosidenib at 500 mg QD was determined to be the RCD for the combination with durvalumab and gemcitabine/cisplatin
- The expansion phase opened using the 500 mg QD dose of ivosidenib and will enroll approximately 40 patients. The objectives are to evaluate the clinical activity and confirm the safety and tolerability of the combination
- As of July 10, 2025, among enrolled patients with at least one post-baseline tumor assessment, 1 (14.3%) patient had a partial response, and 4 (57.1%) patients had stable disease

Conclusions

- The combination of ivosidenib 500 mg QD with durvalumab and gemcitabine/cisplatin demonstrated a safety profile similar to that previously reported for ivosidenib,[6] durvalumab, and gemcitabine/cisplatin[3]
- The 500 mg QD dose of ivosidenib was selected as the RCD
- The expansion phase has opened with the 500 mg QD dose of ivosidenib and will enroll approximately 40 patients to evaluate the clinical activity and confirm the safety and tolerability of the combination

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Patient summary

Background and rationale

The combination of the immunotherapy durvalumab (DURVA) with gemcitabine and cisplatin (GEM/CIS) is a standard initial treatment for cholangiocarcinoma (CCA). This clinical study (NCT06501625) is evaluating the addition of ivosidenib (IVO), an IDH1 inhibitor, to this regimen for patients with mutated *IDH1* advanced or metastatic CCA. The initial safety lead-in phase aimed to determine the safety and recommended dose for the combination.

Methodology

The study enrolled 7 patients with a performance status (ECOG) of 0 or 1. The treatment regimen consisted of IVO 500 mg once daily + DURVA 1500 mg IV infusion every 3 weeks + GEM 1000 mg/m^2 IV and CIS 25 mg/m^2 IV on days 1 and 8 of each cycle every 3 weeks for up to 8 cycles, followed by IVO 500 mg once daily and DURVA 1500 mg every 4 weeks until progression of disease.

Key findings

Safety and tolerability: All 7 patients experienced at least one treatment-emergent adverse event (AE), and 6 patients experienced a grade 3 or higher AE. One dose-limiting toxicity (DLT) occurred—an instance of drug-associated liver injury—which led to treatment discontinuation for that patient. The liver injury resolved after the medication was stopped.

Dosing status: Most patients (6 out of 7) remained on the study at the time of the data cut-off. Dosage interruptions occurred in 4 patients, and 1 required a dose reduction.

Preliminary activity: One patient experienced a partial response and 6 patients experienced stable disease.

Conclusion

The researchers concluded that the safety profile of adding ivosidenib to the DURVA/GEM/CIS regimen is similar to that of the DURVA/GEM/CIS regimen alone. The dose of 500 mg daily of ivosidenib was confirmed for the next phase of the study (expansion phase), which will enroll approximately 40 additional patients to further evaluate efficacy.

The patient summary includes select illustrations designed by Freepik